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## EUROPEAN PATENT APPLICATION

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㉔ Applicant: GAMBRO DIALYSATOREN K.G.,  
Postfach 1323, D-7450 Hechingen (DE)  
Applicant: Gambro Lundia AB, Box 10101, S-220 10 Lund  
(SE)

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㉖ Inventor: Göhl, Hermann Joseph, Ganswies 8,  
D-7457 Bisingen-Zimmern (DE)  
Inventor: Gelling, Günther Friedrich, Lenauweg 2,  
D-7450 Hechingen (DE)  
Inventor: Mayer, Georg Bernhard, Im Egert 18,  
D-7450 Hechingen-Boll (DE)  
Inventor: Gullberg, Claes-Ake, Höstagillesvägen 32,  
S-222 51 Lund (SE)

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㉘ Representative: Boberg, Nils Gunnar Erik, Gambro AB  
Patent Department Box 10101, S-220 10 Lund (SE)

㉙ Filtration membrane and process for producing the membrane.

㉚ Filtration membrane, especially adapted for use in hemofiltration as well as filtration of infusion solutions.

The membrane, preferably in the form of a hollow fiber, is made of a polymer which is soluble in a polar, non-protonic organic solvent. The most preferred polymer for the membrane material is polyamide. Characterizing for the membrane is high ultrafiltration rates (permeabilities to water) of up to  $500 \times 10^{-4}$  ml/sec.  $\times$  cm<sup>2</sup>  $\times$  atm., and impermeability to albumin ( $M_w$  68,000).

The membrane is prepared by extruding a polymer solution with a center liquid under conditions such that the volume of polymer solution to volume of center liquid ratio is within the range of from 2 : 1 to 4 : 1. Simultaneously, the inner diameter to wall thickness ratio of the hollow fiber is preferably correlated to the polymer concentration and is set to 150 : 75 to 280 : 75 at a polymer concentration of 5–20%. The most preferred such correlation is 220 : 75 at a polymer concentration of 11%.

EP 0 098 392 A2

TITLEFILTRATION MEMBRANE AND PROCESS FOR PRODUCING  
THE MEMBRANE5    TECHNICAL FIELD

This invention relates to a filtration membrane which is especially, though not exclusively, adapted for use in hemofiltration.

10   Furthermore, the invention relates to a process for producing a membrane of this type, in which a polymer solution is extruded with a center liquid to form a membrane extrudate which is then optionally washed.

15   It should be clarified that even though the present membrane is especially well adapted for use in hemofiltration, it is not restricted to such an application. It could as well be used in other filtration procedures requiring high flow-through rates such as for example filtration of infusion solutions as it to a large extent rejects endotoxins and pyrogens and most certainly bacteriae and vira. For illustrative purposes only, the 20 following description of the invention will however be concentrated to the former application.

BACKGROUND OF THE INVENTION

25   Hemofiltration membranes are well known in the art. For example, in the U.S. Patent 4 229 291 there is described a polyamide hemofiltration membrane as well as a process for producing the membrane. A similar membrane is described also in the German Patent Publication DE-AS 22 30 36 226. Hemofiltration membranes made of other polymers than polyamide are also known and commercially available. Examples are membranes made of cellulose nitrate (Sartorius; Daicel), polyacrylonitrile (Asahi PAN 15; Rhone-

Poulenc AN 69), polysulphone (Amicon), and polyether-polycarbonate block copolymer (European Patent Application No. 801051185.5).

A common drawback of these known membranes is their relatively low ultrafiltration rates (permeabilities to water), which require that compensating relatively large membrane surface areas are used to obtain at least a minimal required liquid flow-through when the membranes are used in for example hemofiltration. Since the minimal required liquid flow-through is even higher in the filtration of infusion solutions an accordingly larger compensating membrane surface area must therefore be used. To illustrate this, it may be mentioned that a known filtration membrane according to either of U.S. Patent 4 229 291 and German Patent Publication DE-AS 22 36 226, which has an ultrafiltration rate of  $10 - 20 \times 10^{-4}$  ml/sec.  $\times$   $\text{cm}^2 \times$  bar and  $10 - 30 \times 10^{-4}$  ml/sec.  $\times$   $\text{cm}^2 \times$  bar, respectively, will need an available membrane surface area of at least  $0.5 - 1 \text{ m}^2$  to be able to filtrate the required 100 - 200 ml/min. of infusion solution at a transmembrane pressure of 100 - 300 mmHg.

An object of this invention is therefore to provide a filtration membrane which is far better than the known filtration membranes as regards the ability to filtrate liquids at high rates. An especial object is to provide a hemofiltration membrane which in comparison to the known filtration membranes requires only a minimum of compensating surface area to be able to filtrate for example blood at the required flow-through rate.

A further object of the invention is to provide a process for producing the above-mentioned improved membrane according to this invention.

These objects are achieved in accordance with the present invention by means of the membrane and the process as defined in the following claims.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention there is thus provided a filtration membrane, particularly for use in hemofiltration. Said membrane is characterized by  
5 having an ultrafiltration rate (permeability to water) of between  $200 \times 10^{-4}$  and  $500 \times 10^{-4}$  ml/sec.  $\times$   $\text{cm}^2$   $\times$  bar (at  $20^\circ\text{C}$ ) and by being essentially impermeable to albumin ( $M_w$  44,000).

Furthermore, there is provided a process for producing said filtration membrane in the form of a hollow fiber, wherein a polymer solution is extruded with a center liquid to form a membrane extrudate which is then optionally washed. Said process is characterized in that the polymer solution is extruded under conditions such 15 that the volume of polymer solution to volume of center liquid ratio is within the range of from 2:1 to 4:1.

DETAILED DESCRIPTION OF THE INVENTION

The present membrane is an asymmetric, self-supporting membrane and may be in the form of a flat sheet, a tube or a hollow fiber. The hollow fiber shape is the most preferred form.

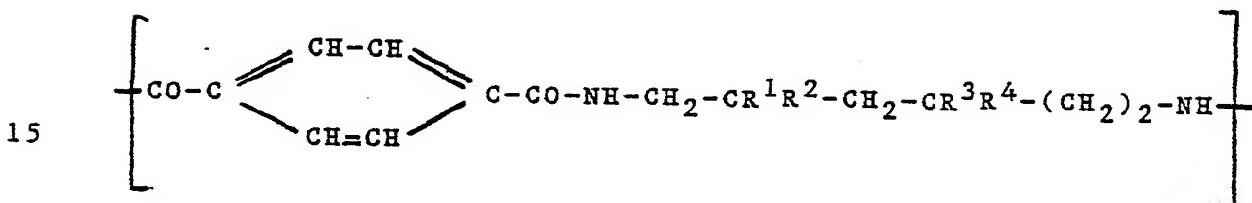
In general, a membrane can be used for hemofiltration if it fulfils the following criteria: non-toxicity, blood compatibility, low tendency for the adsorption of proteins, sharp cut-off, high filtration rates and physical stability. For all these parameters the chemical composition of the membrane material is a major factor, because it greatly influences the membrane structure and 25 it also determines the interaction between blood and membrane.

According to the present invention it has been found that suitable membrane materials which fulfil all of said criteria may be polymers which are soluble in a polar,

non-protonic organic solvent. Examples of such solvents are dimethylsulphoxide (DMSO), dimethylformamide (DMF), and dimethylacetate (DMAc).

Examples of suitable polymers for the present membrane are polysulphone, polyethersulphone, polycarbonate, polyacrylonitrile, polyamide, and polystyrol. The most preferred polymer among these is polyamide.

An example of an especially preferred polyamide according to the present invention is a polyamide having repeating units of the following chemical formula:



wherein R<sup>1</sup> is designating hydrogen and R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> each are designating a (C<sub>1</sub>-C<sub>5</sub>)alkyl group, preferably methyl or wherein R<sup>3</sup> is designating hydrogen and R<sup>1</sup>, R<sup>2</sup> and R<sup>4</sup> each are designating a (C<sub>1</sub>-C<sub>5</sub>)alkyl group, preferably methyl.

The wall thickness of the membrane may vary, but is preferably within the range of from 40 to 100 μm with an inner barrier layer of ca 0.1 μm. The cut-off of the membrane is about 30,000 Daltons.

According to the present invention a membrane of the above-mentioned type is produced by extruding a polymer solution with a center liquid under conditions such that the volume of polymer solution to volume of center liquid ratio is within the range of from 2:1 to 4:1.

Under said process condition it has furthermore been found that an optimum of the membrane characteristics will be obtained, when for example the following two further process conditions are properly adjusted to each other,

namely the inner diameter to wall thickness ratio of the hollow fiber membrane and the polymer concentration of the polymer solution.

According to the present invention said inner diameter to wall thickness ratio may vary within the range of from 150:75 to 280:75, preferably 220:75.

Similarly, said polymer concentration may vary within the range of from 5 to 20%. A polymer concentration outside this range will lead to a membrane which is either too rubbery or which is being inferior as regards the ultrafiltration characteristics. An especially preferred polymer concentration is 11%.

To illustrate the importance of properly adjusting said two further process conditions to each other, when using a volume of polymer solution to volume to center liquid ratio within the above-mentioned range of from 2:1 to 4:1, reference is made to the accompanying figure. In this figure there is shown a graph which as an example is representing the variation of ultrafiltration rate in dependence on the variation of inner diameter to wall thickness ratio. In the shown example the wall thickness is invariable (75  $\mu\text{m}$ ) and the used polymer concentration is 11%.

From this illustrated example it can be seen that an increasing of the inner diameter to wall thickness ratio - at an invariable wall thickness - the ultrafiltration rate of the hollow fiber membrane is increasing. In the illustrated inner diameter to wall thickness ratio of 2 - 4 said ultrafiltration rate is increasing along a straight line according to the relation:

$$\text{ultrafiltration rate} = k \times \text{inner diameter/outer diameter}$$

Furthermore, it has been found that with increasing ultrafiltration rate within the illustrated range the cut-off of the membrane is not (as was expected) increasing to higher cut-off values, but is rather invariably fixed at about 30,000 Daltons. Furthermore, it was found that the membrane characteristics as regards the cut-off were uniform at higher inner diameter : wall thickness ratios.

The above illustrated unexpected phenomena could be explained thereby that at higher inner diameter to wall thickness ratios more precipitating agent, as calculated with reference to the polymer concentration, is available and that the polymer solution therefore will precipitate more rapidly. This will lead to a more uniform inner barrier layer of the membrane wall structure. It is known in the art that the pore size, pore distribution and occurrence in the barrier layer have influences on the cut-off value and the ultrafiltration characteristics of the membrane. Within the present inner diameter to wall thickness ratio is apparently obtained a very high occurrence and uniformity of the inner barrier layer.

For example, at an inner diameter to wall thickness ratio of 200:75 and a polymer concentration of 11% the ultrafiltration rate of the membrane will be inferior to  $100 \times 10^{-4} \text{ ml/cm}^2 \times \text{ atm.}$  while the ultrafiltration rate is about  $400 \times 10^{-4} \text{ ml/sec.} \times \text{ cm}^2 \times \text{ atm.}$  at an inner diameter to wall thickness ratio of 250:75.

Especially, it has been found that at an inner diameter to wall thickness ratio of 220:75 and a polymer concentration of 11% the maximal ultrafiltration rates (up to  $500 \times 10^{-4} \text{ ml/sec.} \times \text{ cm}^2 \times \text{ atm.}$ ) and simultaneously good retention capability for high molecular weight proteins can be obtained. One provision for the high-permeable membranes in the extrusion process is that the

polymer solution after leaving the die and before reaching a first wash bath is completely exchanged by the center liquid from inside of the hollow fiber, i.e. the residence time in the ambient atmosphere before the hollow fiber 5 extrudate reaches said first wash bath must involve a minimum of time and the distance between the die and the wash bath must be at least a minimal distance.

For example, when said distance between the die and the wash bath is at least 1 meter said minimal residence 10 time is about 2 sec. in the ambient atmosphere (at a hollow fiber production rate of 30 meters/minute) before the hollow fiber extrudate is introduced into the wash bath. After this residence time the hollow fiber extrudate is completely formed from inside, i.e. the hollow fiber 15 extrudate will not be effected by the wash bath. Consequently, there will be formed no outer barrier layer, which will be the case if the residence time under the given conditions is too short.

Examples of polymers for said polymer solution may be 20 the polymers mentioned above, and examples of suitable solvents may be DMSO, DMF, DMAc or similar polar, non-protonic organic solvents. Water may be used as said center liquid, preferably deionized water.

The polymer solution viscosity is generally from 100 25 to 3,000 cps, preferably 300 cps, as measured at 20°C.

The invention will be further illustrated by the following non-restricting examples.

#### Example 1

30 11% of a polyamide was dissolved in DMSO at room temperature, and the solution was filtered and degassed. The polymer solution viscosity was 300 cps.

The polymer solution (105 ml/h) was extruded with 35 ion-free water as a center liquid (50 ml/h) through an annular die to form a hollow fiber extrudate having an inner diameter of 190 µm and an outer diameter of 340 µm.

After passing a height of fall (1 meter) through the ambient atmosphere the hollow fiber extrudate was introduced in a first wash bath and consecutively through following wash baths of different temperatures with 5 different residence times, until the solvent had been completely washed out.

The obtained hollow fiber according to this example has the following characteristics:

Hydraulic permeability ( $20^{\circ}\text{C}$ ):  $80 \times 10^{-4} \text{ ml/sec.} \times \text{cm}^2 \times 10 \text{ atm.}$

Retention capability for Ov-albumin ( $M_w$  44,000): 98%

Retention capability for human albumin ( $M_w$  68,000): 100%

#### Example 2

15 The same process conditions as in Example 1 were used. The dimensions of the hollow fiber varied by varying the volume rates of center liquid (88 ml/h) and polymer solution (126 ml/h). The inner diameter of the hollow fiber was 250  $\mu\text{m}$  and the outer diameter was 400  $\mu\text{m}$ .

20 The obtained hollow fiber had the following characteristics:

Hydraulic permeability ( $20^{\circ}\text{C}$ ):  $400 \times 10^{-4} \text{ ml/sec.} \times \text{cm}^2 \times 10 \text{ atm.}$

Retention capability for Ov-albumin ( $M_w$  44,000): 98%

25 Retention capability for human albumin ( $M_w$  68,000): 100%

#### Example 3

30 The same process conditions as in Example 1 were used. The dimensions of the hollow fiber were varied by varying the volume rate of center liquid (64 ml/h) and polymer solution (110 ml/h). The inner diameter of the hollow fiber was 220  $\mu\text{m}$  and the outer diameter was 370  $\mu\text{m}$ .

The obtained hollow fiber had the following characteristics:

Hydraulic permeability (20°C):  $200 \times 10^{-4}$  ml/sec.  $\times$   $\text{cm}^2$   $\times$  atm.

Retention capability for Ov-albumin ( $M_w$  44,000): 98%

Retention capability for human albumin ( $M_w$  68,000): 100%

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When used in a hemofilter having an effective membrane surface area of  $1.16 \text{ m}^2$  and an effective hollow fiber length of 25 cm, this hollow fiber had a filtration performance for blood (25% Hct, 70 mg/l total albumin, 10 37°C) of 120 ml/min. The blood flow rate was 350 ml/min.

When used as an infusion solution filter having a surface area of  $0.1 \text{ m}^2$  and an effective hollow fiber length of 10 cm, this hollow fiber filtered 300 ml/min. of infusion solution at a transmembrane pressure of 200 mmHg.

15 When the filtered infusion solution contained 1,000 ng/l endotoxins, no endotoxins could be detected in the filtrate. Detectable limit 0.05 ng/l. Examples of such tested endotoxins are E-Coliendotoxin and Lysate IGQ having molecular weights of between 50,000 and  $1 \times 10^6$  Daltons.

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#### INDUSTRIAL APPLICABILITY

The present filtration membrane is particularly though not exclusively, adapted for use in hemofiltration. In general, the membrane can be used in any other filtration procedures requiring high flow-through rates, such as 25 for example filtration of infusion solutions. More in general, the membrane can be used in applications requiring that the membrane fulfills the following criteria: non-toxicity, blood compatibility, low tendency for the 30 adsorption of proteins, sharp cut-off, high filtration rates and physical stability.

CLAIMS

1. Filtration membrane, characterized by having an ultrafiltration rate (permeability to water) of between  $200 \times 10^{-4}$  and  $500 \times 10^{-4}$  ml/sec. cm<sup>2</sup> bar at 20°C and by  
5 being essentially impermeable to human albumin.  
(M<sub>w</sub> 44,000).

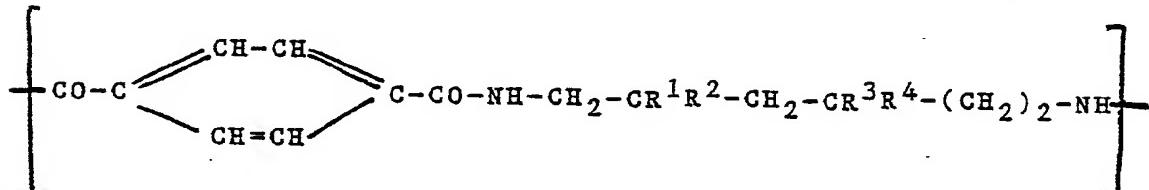
2. Membrane according to claim 1, characterized by being in the form of a hollow fiber.

3. Membrane according to claim 1 or 2, characterized  
10 by being manufactured of a biocompatible polymer which is soluble in a polar, non-protonic organic solvent.

4. Membrane according to claim 3, characterized in that said polymer is chosen among polysulphone, polyether sulphone, polycarbonate, polyacrylonitrile, polyamide, and  
15 polystyrol, preferably polyamide.

5. Membrane according to claim 3 or 4, characterized in that said polymer is a polyamide having repeating units of the following chemical formula:

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wherein R<sup>1</sup> is designating hydrogen and R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> each are designating a lower-alkyl group, or wherein R<sup>3</sup> is designating hydrogen and R<sup>1</sup>, R<sup>2</sup> and R<sup>4</sup> each are designating a lower-alkyl group.

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6. Membrane according to any of the preceding claims, characterized by having a wall thickness of from 40 to 100 µm and by having a cut-off of 30,000 Daltons.

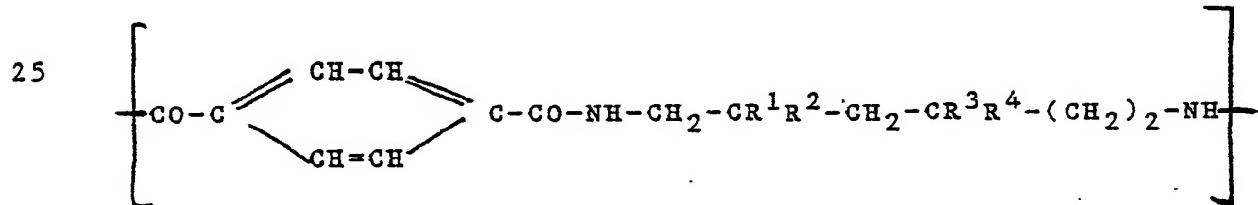
7. Process for producing a filtration membrane according to any of claims 1 - 6, wherein a polymer solution is extruded with a center liquid to form a membrane extrudate which is then optionally washed, 5 characterized in that said polymer solution is extruded under conditions such that the volume of polymer solution to volume of center liquid ratio is within the range of from 2:1 to 4:1.

8. Process according to claim 7, characterized in 10 that said polymer solution is containing 5-20% of a polymer which is soluble in a polar non-protonic organic solvent.

9. Process according to claims 8, characterized in 15 that said polymer solution is containing 11% of said polymer.

10. Process according to any of claims 7 - 9, characterized in that said polymer is chosen among polysulphone, polyether sulphone, polycarbonate, polyacrylonitrile, polyamide, and polystyrol, preferably polyamide.

20 11. Process according to claim 10, characterized in that said polymer is a polyamide having repeating units of the following chemical formula:



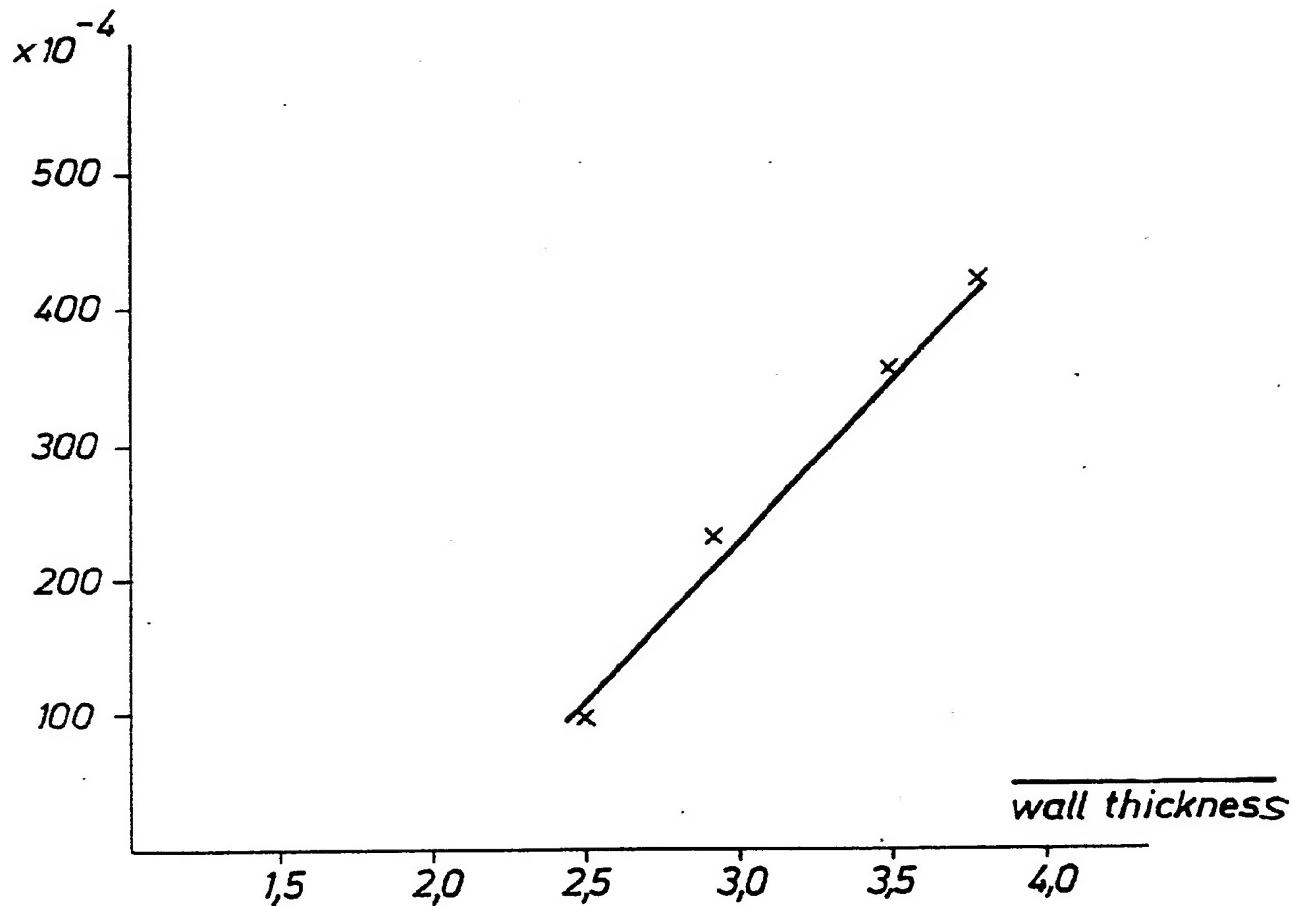
30 wherein R<sup>1</sup> is designating hydrogen and R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each designating a (C<sub>1</sub>-C<sub>5</sub>)alkyl group, preferably methyl, or wherein R<sup>3</sup> is designating hydrogen and R<sup>1</sup>, R<sup>2</sup> and R<sup>4</sup> are each designating a (C<sub>1</sub>-C<sub>5</sub>)alkyl group, preferably methyl.

12. Process according to any of claims 7 - 11, characterized in that said polymer solution has a viscosity of from 100 to 3,000 cps, preferably 300 cps, as measured at 20°C.

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Ultrafiltration rate [ $m'/sec. cm^2 at$ ]





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(72) Inventor: Göhl, Hermann Joseph  
Ganswies 8  
D-7457 Bisingen-Zimmern(DE)

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(72) Inventor: Geiling, Günther Friedrich  
Lenauweg 2  
D-7450 Hechingen(DE)

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(72) Inventor: Mayer, Georg Bernhard  
Im Egert 18  
D-7450 Hechingen-Boll(DE)

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(72) Inventor: Gullberg, Claes-Ake  
Höstagillesvägen 32  
S-222 51 Lund(SE)

(71) Applicant: GAMBRO DIALYSATOREN K.G.  
Postfach 1323  
D-7450 Hechingen(DE)

(74) Representative: Boberg, Nils Gunnar Erik  
Gambro AB Patent Department Box 10101  
S-220 10 Lund(SE)

(71) Applicant: Gambro Lundia AB  
Box 10101  
S-220 10 Lund(SE)

(54) Filtration membrane and process for producing the membrane.

(57) Filtration membrane, especially adapted for use in hemofiltration as well as filtration of infusion solutions.

The membrane, preferably in the form of a hollow fiber, is made of a polymer which is soluble in a polar, non-protonic organic solvent. The most preferred polymer for the membrane material is polyamide. Characterizing for the membrane is high ultrafiltration rates (permeabilities to water) of up to  $500 \times 10^{-4}$  ml/sec. x cm<sup>2</sup> x atm., and impermeability to albumin (M<sub>w</sub> 68,000).

The membrane is prepared by extruding a polymer solution with a center liquid under conditions such that the volume of polymer solution to volume of center liquid ratio is within the range of from 2:1 to 4:1. Simultaneously, the inner diameter to wall thickness ratio of the hollow fiber is preferably correlated to the polymer concentration and is set to 150:75 to 280:75 at a polymer concentration of 5 - 20%. The most preferred such correlation is 220:75 at a polymer concentration of 11%.

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# EUROPEAN SEARCH REPORT

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. <sup>3</sup> )
A	US-A-4 181 694 (Y. HASHINO et al.) * Column 8, lines 35-50; examples 1-30; tables 3-12 *	1-4,7-10,12	B 01 D 13/04 A 61 M 1/03
D,A	US-A-4 229 291 (A. WALCH et al.)  * Claim 1, column 6, lines 58-68; examples 1-5 *	1,3-6,8,10-12	
A	DE-A-2 827 012 (ASAHI KASEI KOGYO) * Claim 1 *	1,2	
A	DE-A-2 829 630 (ASAHI KASEI KOGYO) * Claims 1, 7, 8, 11, 16; examples 1-6 *	1-4,7-10	TECHNICAL FIELDS SEARCHED (Int. Cl. <sup>3</sup> )
A	DE-A-2 921 138 (ASAHI MEDICAL)  * Claims 1, 5; page 9, lines 15-16; page 10, lines 11-14; examples 1-10 *	1-4,6-8,10, 12	A 61 M 1/03 B 01 D 13/00 B 01 D 13/04 D 01 D 5/06 D 01 D 5/24 D 01 D 5/247 D 01 F 1/08 D 01 F 6/60 D 01 F 6/90
The present search report has been drawn up for all claims			
Place of search BERLIN	Date of completion of the search 28-10-1983	Examiner KUEHN P	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone	Y : particularly relevant if combined with another document of the same category		
A : technological background	O : non-written disclosure		
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Page 2

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. <sup>2</sup> )
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<p>JOURNAL OF APPLIED POLYMER SCIENCE, vol. 21, 1977 I. CABASSO et al. "Porosity and pore size determination in polysulfone hollow fibers", pages 1883-1900 * Tables 1, 2 *</p> <p>-----</p>	1	
TECHNICAL FIELDS SEARCHED (Int. Cl. <sup>3</sup> )			
The present search report has been drawn up for all claims			
Place of search <b>BERLIN</b>	Date of completion of the search <b>28-10-1983</b>	Examiner <b>KUEHN P</b>	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			